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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/033,571	12/27/2001	Shuyuan Zhang	29853/37702	9714

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EXAMINER	
BLUMEL, BENJAMIN P	
ART UNIT	PAPER NUMBER
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/033,571	ZHANG ET AL.	
	Examiner	Art Unit	
	Benjamin P. Blumel	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70-72,74-77 and 79-162* is/are pending in the application.

4a) Of the above claim(s) *99-128* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70-72,74-77,79-98 and 129-162* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/25/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant is notified that Benjamin Blumel is now conducting examination of this application. Correspondence information is stated below.

Any rejections not stated below are withdrawn from consideration.

Claims 99-128 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on September 26, 2006.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on September 5, 2006 was filed after the mailing date of the non-final rejection on May 2, 2006. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Based on Applicant's amendments to claim 1 which now states "adenovirus composition having a contaminating nucleic acid content of less than 400 pg 10^{10} pfu virus and greater than or equal to about 60 pg per 10^{10} pfu virus", the following new rejection is made with regard to the existing claimed invention as discussed below. Applicant's arguments with respect to the

rejection under 35 USC § 103 as being unpatentable over Garnier et al., Perrin et al., Morris et al. and Gilbert et al. have been considered but are moot in view of the new ground(s) of rejection.

Claims 70-72, 74-77, 79-98 and 129-161 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shabram et al. (US 5,837,520), Huyghe et al. (Human Gene Therapy, 1995), Kozak et al. (Developments in Biological Standardization, 1996), Keay et al. (Biotechnology and Bioengineering, 1976), Nadeau et al. (Biotechnology and Bioengineering, 1996) and Griffiths J.P. (Animal Cell Biotechnology, 1986).

The instant invention is drawn a method purifying a recombinant replication-incompetent adenovirus by replicating the recombinant virus in 293 cells in a bioreactor, grown on microcarriers in serum-free media. Specifically, the claimed method does not involve a cesium chloride density gradient centrifugation step, but does involve providing the necessary nutrients via perfusion, fed-batch or in automated roller bottles. Furthermore, The adenovirus of the instant invention lacks at least a portion of the E1 region and contains the CMV IE promoter, which is linked to the therapeutic gene p53. In addition, the isolated virus is purified with at least one chromatography step following the removal of contaminating nucleic acid by treatment with a nuclease. The purified adenovirus composition comprises 70%+/- 10% of the starting pfu, is characterized by having a small amount of contaminating nucleic acid, such as less than 0.2 or 0.8 ng/ml, about 60pg to 400pg per 10^{10} pfu of virus, has a BSA content below the detection level of western blot analysis and has an absorbance A_{260}/A_{280} of 1.27+/- 0.03 or between 1.2 and 1.3. In addition, the purified recombinant virus is suspended in a pharmaceutically acceptable buffer, the viral composition provides a unit dose of 10^3 to 10^{15} or 10^{10} to 10^{14} pfu/dose and the particle to pfu ratio is about 36 to about 38.

The teachings of Shabram et al. have been made of record. In addition, Shabram et al. state a yield of 49%-65% post-column purification and that the particle to pfu ratio can "vary widely" from preparation to preparation. In view of the argument set forth by the applicants that Shabram et al. do not teach the reduction of contaminating nucleic acid to the levels presently claimed, Shabram et al. do state that the use of Benzonase, a highly efficient nuclease, could reduce or eliminate the presence of such nucleic acids from their Adenovirus preparation. These statements are supported by documented activity of Benzonase®, the nuclease of US (5,173,418), with regard to its ability to degrade contaminating nucleic acids as reported in (Novagen® & Calbiochem®, Sample Preparation Tools for Protein Research, 2nd Edition, 2006) and (Sastry et al., Human Gene Therapy, 2004). Furthermore, upon further review of the specification of the instant application, it would appear that no additional steps were conducted as compared with those of Shabram et al. except for the isotope labeled DNA probe utilized in determining residual contaminating nucleic acids. Therefore, the steps followed by Shabram et al. in order to remove contaminating nucleic acids are functionally similar as in the instant application and would result in an adenovirus preparation with similar levels of contaminating nucleic acids, if any at all. However, Shabram et al. do not teach the use of western blot to detect BSA levels, the use of serum-free media to culture the adenovirus on microcarriers in a fed-batch, perfusion or automated culture system, or the specific pfu dosages of 10^3 to 10^{15} or 10^{10} to 10^{14}.

Huyghe et al. teach the purification of adenovirus by multiple steps, including cesium gradient, followed by multiple column purifications. During the course of purification, samples were analyzed with regard to particles to pfu ratios. It was determined that initially, cesium

gradient ratios ranged from 20 (+/-7)-130 (+/-45):1, followed by 60 (+/-21):1 for the crude lysate, and 82 (+/- 29):1 after single column chromatography.

Kozak et al. discuss the importance of monitoring the origin of bovine specimens in order to track and prevent possible BSE/TSE contamination, specifically focusing on biological/biopharmaceutical production protocols that utilize bovine specimens.

Keay et al. teach the development of serum-free cell culture media for established cell lines and for the production of viruses. Keay et al. discusses the adaptation of serum-free media due to the expense of tissue culture serum and the risks of contamination. Keay et al. were able to culture Adenovirus-2 in HeLa and KB cells in serum-free media. Keay et al. observed similar virus yields between serum-free media and complete media.

The teachings of Nadeau et al. have been made of record. The argument set forth by the applicants that Nadeau et al. do not teach the production of adenovirus itself is recognized. However, Nadeau et al. discuss the scale-up of adenovirus preparations needed for gene therapy in the range of 10^{12}-10^{13} pfu in certain cases to transduce the target cell/tissue/organ. The teachings of Nadeau et al. set forth a simple method of mass volume tissue culture involving recombinant, replication defective adenovirus through a fed-batch system.

Griffiths J.P. discuss the importance of using microcarriers in scale-up tissue culture systems to increase surface area for attachment dependent cells. The use of such microcarriers would result in a significant increase of the cell population and subsequent yield of required product.

It would have been obvious to one of ordinary skill in the art to modify the methods taught by Shabram et al. in order to make a purified adenovirus of the instant invention thereby

decreasing the amount of BSA, contaminating nucleic acids and increasing the cell density by use of microcarriers in a fed-batch system. One would have been motivated to do so, given the suggestion by Shabram et al. to produce a pure adenovirus preparation at a high titer for pharmaceutical usage. There would have been a reasonable expectation of success, given the knowledge that the ability to grow cells and produce adenovirus without serum has many benefits since serum is expensive and contamination for example with bovine infectious agents is of great concern, as taught by Keay et al. and Kozak et al., also given the knowledge large amounts of recombinant adenovirus are required for effective gene therapy and that particle to pfu ratios vary among preparations, as taught by Nadeau et al. and Huyghe et al., and also given the knowledge that when culturing large amounts attachment dependent cells, microcarriers provide additional surface area to maximize the volume of media. Furthermore, the teachings of Keay et al. provided an adenovirus preparation without serum in culture and therefore BSA would not be detected by Western blot analysis. In addition, the teachings of Huyghe et al. and Shabram et al. with regard to the variability of particle to pfu ratios are also supported since harvesting of matures virions is variable depending on culture conditions and length of incubation post infection (i.e. empty viral particles can form and harvested when cells are mechanically disrupted). Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Summary

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Benjamin P. Blumel whose telephone number is 571-272-4960. The examiner can normally be reached on M-F, 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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